Impact of Different Iterations of Devices and Degree of Aortic Valve Calcium on Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation

William K.F. Kong, MD[a,b], Philippe J. van Rosendael, MD[a], Frank van der Kley, MD[a], Arend de Weger, MD[c], Vasileios Kamperidis, MD, PhD[a], Madelien V. Regeer, MD[a], Nina Ajmone Marsan, MD, PhD[a], Jeroen J. Bax, MD, PhD[a], and Victoria Delgado, MD, PhD[a,*]

The iterations of the SAPIEN prosthesis might impact the incidence and grade of paravalvular regurgitation (PVR). The aim of this study was to assess the impact of iterations of balloon-expandable valves (SAPIEN, SAPIEN XT, and SAPIEN 3) and degree of aortic valve calcification (AVC) on the severity of PVR after transcatheter aortic valve implantation (TAVI). Comprehensive echocardiographic examinations and multidetector computed tomography (MDCT) were performed in 272 patients (127 men, 81 ± 7 years old, logistic EuroScore of 21 ± 13%) who underwent TAVI with 23- and 26-mm balloon-expandable valves. The degree of AVC was assessed with MDCT. PVR grade was assessed with echocardiography. The cover index was calculated as (prosthesis area − MDCT annulus area)/prosthesis area. SAPIEN, SAPIEN XT, and SAPIEN 3 prostheses were implanted in 103 patients (38%), 105 patients (38.5%), and 64 patients (23.5%), respectively. Significant PVR (≥moderate) occurred in 14%, 10%, and 0% of patients receiving the SAPIEN, SAPIEN XT, and SAPIEN 3, respectively ($p = 0.010$). Across the groups, the aortic annulus size, degree of calcification, and cover index were comparable. Larger burden of AVC was independently associated with significant PVR (odds ratio 3.48, $p = 0.006$) after adjusting for age, body surface area, gender, aortic annulus area, cover index, and prosthesis iteration. SAPIEN 3 was associated with lower frequency of significant PVR (odds ratio 0.31, $p = 0.002$). In conclusion, the incidence of significant PVR significantly decreased over time with improvement in valve design. SAPIEN 3 was associated with less significant PVR after TAVI independently of the AVC burden. **(Am J Cardiol 2016;118:567−571)**

The SAPIEN 3 THV (S3-THV; Edwards Lifesciences Inc, Irvine, California) is the newest generation of balloon-expandable bioprosthetic aortic valve, which received US Food and Drug Administration approval in June 2015 for treatment of patients at high risk with severe, symptomatic aortic stenosis (AS) (Figure 1). The SAPIEN 3 valve has been associated with lower incidence of significant paravalvular regurgitation (PVR) in a multicenter registry recently.[1,2] The new features of this device, a new cobalt-chromium frame with large cell design containing the valve and an outer polyethylene terephthalate cuff enhance the sealing of the aortic annulus and the gaps between the prosthetic frame and the native valve caused by the presence of extensive, asymmetric bulky calcific deposits.[3] The effect of valve iterations and degree of aortic valve calcification (AVC) on the severity of PVR after transcatheter aortic valve implantation (TAVI) has not been evaluated. The aim of this study was to investigate the impact of iteration of these balloon-expandable valves (SAPIEN, SAPIEN XT, and SAPIEN 3) and degree of AVC on the PVR severity in patients with severe AS.

Methods

From November 2007 till June 2015, all patients with symptomatic severe AS treated with balloon-expandable transcatheter aortic bioprostheses (SAPIEN, SAPIEN XT, and SAPIEN 3) at the Leiden University Medical Center were included. Patients receiving self-expandable valves, 29-mm balloon-expandable prosthesis or undergoing valve-in-valve procedures were excluded from this study. Patients deemed too high risk for surgical options with high logistic EuroSCORE and contraindications for surgery (porcelain aorta, frailty, severe chronic obstructive airway disease, and previous coronary artery bypass grafting) were referred for TAVI. Demographics, clinical, echocardiographic, multidetector row computed tomographic (MDCT) data and procedure data were prospectively collected in our center database (EPD Vision, version 8.3.3.6; Leiden, the Netherlands) for retrospective analysis.

All the TAVI candidates underwent detailed clinical and imaging workup. Either a 64-detector or 320-detector row

Departments of [a]Cardiology and [c]Cardiothoracic surgery, Leiden University Medical Center, Leiden, the Netherlands; and [b]Department of Cardiology, National University Heart Centre, Singapore, Singapore. Manuscript received February 13, 2016; revised manuscript received and accepted May 23, 2016.

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*Corresponding author: Tel: (+31) 71-526-2020; fax: (+31) 71-526-6809.

E-mail address: v.delgado@lumc.nl (V. Delgado).

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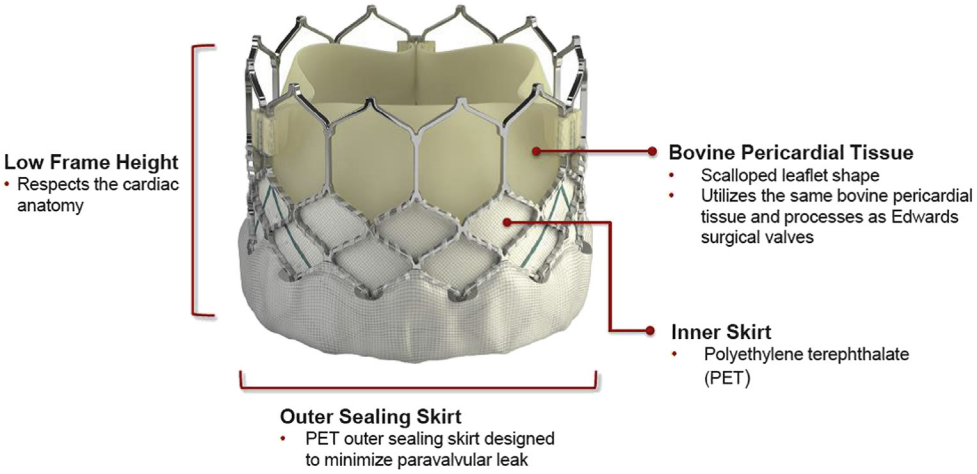

Figure 1. Edward SAPIEN 3 transcatheter heart valve. The new SAPIEN 3 valve is characterized for a low frame height, including an inner and an outer sealing skirt to reduce the PVR. Courtesy of Edwards Lifesciences (https://edwardslifesciences.box.com/s/1yxhofw4adrqkeimz2vyjc99jmuy0jmz).

Table 1
Baseline and echocardiographic characteristics before transcatheter aortic valve implantation

Variable	Sapien (n=103)	Sapien XT (n=105)	Sapien 3 (n=64)	p-value
Age, (years)	81 ± 7.5	81 ± 6.2	81 ± 5.1	0.756
Male	54 (52%)	49 (47%)	29 (45%)	0.595
Body surface area (m^2)	1.82 ± 0.18	1.82 ± 0.18	1.81 ± 0.20	0.867
Sinus rhythm/atrial fibrillation/pacemaker	71 (69%) / 19 (18%) / 13 (13%)	78(74%) / 16 (15%) / 11 (11%)	42 (66%) / 16 (25%) / 6 (9%)	0.572
Hypertension	81 (79%)	76 (72%)	49 (77%)	0.566
Diabetes mellitus	31 (30%)	26 (25%)	19 (30%)	0.650
Hypercholesterolemia	81 (79%)	77 (73%)	43 (67%)	0.258
Previous myocardial infarction	29 (28%)	19 (18%)	9 (14%)	0.061
Previous coronary bypass grafting	45 (44%)	23 (22%)	23 (36%)	0.018
Preoperative creatinine (μmol/L)	108 ± 60	93 ± 34	100 ± 54	0.116
Estimated glomerular filtration rate (ml/min/1.73m^2)	63 ± 23	69 ± 23	68 ± 25	0.138
Haemoglobin, (mmol/L)	7.6 ± 1.0	7.7 ± 1.1	8.0 ± 1.4	0.057
Logistic EuroSCORE (%)	24.8 ± 13.3	21.0 ± 13.6	15.5 ± 7.9	<0.001
Echocardiography				
Left ventricular ejection fraction, %	52.2 ± 14.3	55.6 ± 14.8	58.4 ± 15.6	0.029
Aortic valve area, (cm^2/m^2)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.994
Mean aortic gradient, (mmHg)	39.5 ± 16.0	43.9 ± 18.7	41.8 ± 15.2	0.164
Maximal aortic gradient, (mmHg)	64.1 ± 24.1	71.9 ± 28.6	67.4 ± 23.8	0.095
Medications				
β-blockers	65 (63%)	69 (66%)	42 (66%)	0.911
Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers	63 (61%)	59 (56%)	27 (42%)	0.053
Diuretics	75 (73%)	65 (62%)	34 (53%)	0.031
Calcium channel blocker	33 (32%)	29 (28%)	12 (19%)	0.171
Statins	78 (76%)	60 (57%)	35 (55%)	0.005
Aspirin	55 (53%)	59 (56%)	31 (48%)	0.619
Oral anticoagulants	38 (37%)	29 (28%)	19 (30%)	0.331

computed tomography scanner (Aquilion 64 and Auilion ONE, respectively; Toshiba Medical Systems, Otawara, Japan) was used to assess the aortic annular size, the dimension of all the segments of the aorta, the degree and location of the AVC, and the anatomy of the peripheral arteries. The MDCT data acquisition protocol for the Aquilion 64 and Aquilion ONE has been previously described.[4] Patients with heart rate more than 65 beats/min received either an oral beta blocker (50 to 100 mg metoprolol), unless contraindicated. Scanning was performed during midinspiratory breath-holding. The arrival of bolus media was detected using a real-time tracking technique with a threshold of +180 Hounsfield units. All the MDCT data were recorded and stored for postprocessing. Aortic

Table 2
Procedural and imaging characteristics of the population

Variable	Sapien (n=103)	Sapien XT (n=105)	Sapien 3 (n=64)	p-value
Transapical	62 (60%)	71 (68%)	15 (23%)	<0.001
Sapien Prosthesis size				0.022
23 mm	23 (22%)	35 (33%)	27 (42%)	
26 mm	80 (78%)	70 (67%)	37 (58%)	
Intraprocedural grade of paravalvular regurgitation ≥moderate	14 (14%)	10 (10%)	0	0.010
Aortic annulus area derived from MDCT, (mm^2)	443 ± 87	444 ± 68	427 ± 65	0.293
Cover index, (%)	11.97 ± 15.45	9.52 ± 11.23	11.39 ± 8.48	0.344
Agatston calcium score of the aortic valve				
Mean	3061 ± 1468	3194±1981	3129±1449	0.850
Median	2771 [1940-4070]	2723 [1806-4089]	2860 [2129-4124]	0.859

MDCT = multidetector row computed tomography.

annulus dimensions (perimeter, maximum diameter, minimum diameters, and aortic valve area) were measured according to the standard protocol.[5] For quantitative assessment of AVC, Agatston score of the aortic valve was assessed (including a volume from the aortic annulus until the level of the coronary ostia including left ventricular outflow tract [LVOT]).[6] The cover index was calculated as (prosthesis area−MDCT annulus area)/prosthesis area, as previously described.[7] Comprehensive transthoracic echocardiography was performed before TAVI with a commercially available ultrasonographic system (Vingmed Vivid; General Electric Vingmed, Horten, Norway). Valve morphology, AS severity, and left ventricular (LV) function were measured according to the European Association of Cardiovascular Imaging/American Society of Echocardiography standards.[8] LV ejection fraction was calculated by the Simpson's biplane method. For quantification of aortic valve regurgitation, the jet deceleration slope (pressure halftime), jet width or jet area, vena contracta, and the diastolic flow reversal in the descending aorta were considered in an integrative approach.[9]

TAVI was performed through transfemoral or transapical approach, based on the feasibility of the iliofemoral anatomy and suitable access sites. All procedures were performed in a fully equipped hybrid cardiac catheterization laboratory. Surgical cutdown or suture-mediated closure device (Perclose ProGlide; Abbott laboratories, Abbott Park, Illinois) were used to close the vascular access site at the femoral arteries. All procedures were performed under general anesthesia. Transesophageal echocardiography was used to support TAVI procedures, and fluoroscopy was used to guide the deployment of the valves and prosthesis positioning. Both predilatation of the native valve and prosthetic valve implantation were performed during rapid right ventricular pacing (160 to 200 beats/min) as previously described.[10] Prosthesis position, function, and coronary ostia patency were assessed with transesophageal echocardiography and fluoroscopy. After implantation of the TAVI bioprosthesis, the presence and severity of aortic regurgitation (both transvalvular and paravalvular) was assessed with transesophageal echocardiography and classified according to the Valve Academic Research Consortium (VARC)-2 recommendations.[11] The severity of the PVR was classified as none, trace, mild, moderate, and severe.

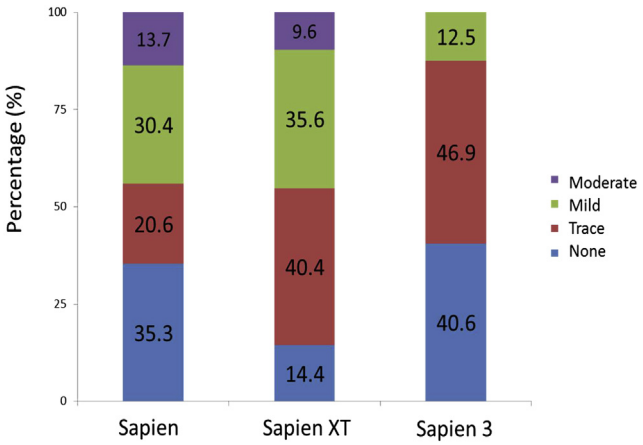

Figure 2. PVR evaluated by transeosophageal echocardiography immediately after TAVI. Note the significant reduction in moderate and severe PVR frequency after TAVI (13.7% in the SAPIEN group, 9.6% in the SAPIEN XT, and 0% in the SAPIEN 3 group; p = 0.01).

The circumferential extend of the PVR was assessed in the parasternal short-axis views with color Doppler.[12,13] The localization and severity of the PVR was judged in the midesophageal and transgastric views. Moderate or higher grade of PVR was treated with further postdilatation or second valve implantation, with agreement among the Heart Team members present during the procedure.

Continuous variables are expressed as mean ± SD or as median (interquartile range) if not normally distributed. Categorical variables are presented as frequency and percentage. For comparison of continuous variables, the Student *t* test, 1-way analysis of variance (with Bonferroni post hoc analysis), or the Mann−Whitney *U* test were used, as appropriate. For comparison of categorical variables, the chi-square test was used. Univariate and multivariate binary logistic regression analyses were performed. Odds ratios and 95% CIs were reported. Statistical analysis was performed using SPSS software, version 20 (IBM Corp, Armonk, New York). A p value <0.05 defined statistical significance.

Results

Baseline characteristics, echocardiographic features, and medication use of 272 patients (mean age 81 ± 7 years, 52%

Table 3
Univariate and multivariate associates of PVR after TAVI

Variable	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Aortic annulus area derived from MDCT, (mm^2)	1.006 (1.000-1.011)	0.045	0.997 (0.988-1.006)	0.480
Cover index, (%)	0.016 (0.001-0.387)	0.011	0.012 (0.000-2.038)	0.083
Log transformed Agatston calcium score	2.997 (1.318-6.817)	0.009	3.478 (1.424-8.498)	0.006
SAPIEN 3 valve	0.381 (0.194-0.749)	0.005	0.306 (0.146-0.642)	0.002

MDCT = multidetector row computed tomography.

women) are presented in Table 1. The SAPIEN valve was implanted in 103 patients (38%), 105 patients (39%) received a SAPIEN XT, and 64 patients (24%) received a SAPIEN 3. The SAPIEN 3 group had a lower percentage of patients with previous coronary artery bypass grafting, lower logistic EuroScore, more preserved LV ejection fraction, and lower number of patients using diuretics or statins than the other groups (Table 1).

The MDCT and procedural characteristics for each group are illustrated in Table 2. There were no differences in the aortic annulus area, percentage of cover index, and both mean and median Agatston calcium score of the aortic valve between the 3 groups. However, the transapical access was more frequently used in the SAPIEN and SAPIEN XT groups than in the SAPIEN 3 group. Furthermore, the 23-mm valve was more frequently used in the SAPIEN 3 group than their counterparts (Table 2).

In terms of procedural results, a significant difference in PVR grade was noted across groups, with a significant reduction in the number of patients with $\geq$ moderate PVR (14% in the SAPIEN group, 10% in the SAPIEN XT, and 0% in the SAPIEN 3 group; $p = 0.01$; Table 2 and Figure 2). To investigate the impact of TAVI valve iteration on the risk of $\geq$ moderate post-TAVI PVR, a multivariate regression analysis was performed. After correcting for aortic annulus dimensions and cover index, AVC burden and TAVI bioprosthesis were independently associated with $\geq$ moderate PVR, whereas increasing amount of AVC was associated with higher risk of significant PVR, the iteration SAPIEN 3 was associated with lower risk suggesting that the new design features of this valve may counteract the effects of the AVC burden (Table 3).

Discussion

The principal finding of this study is that the incidence of significant PVR decreased over time with the improvement of the bioprosthesis design. The SAPIEN 3 valve was independently associated with lower frequency of significant PVR independently of degree of AVC.

The amount and location (symmetric vs asymmetric) of AVC are important correlates of PVR after TAVI.[4,14] It has been hypothesized that AVC plays a role in anchoring and achieving better positioning of balloon-expandable valves. However, excessive or asymmetric distribution of calcification may lead to significant PVR.[15] The present study demonstrated that excessive calcification of the native aortic valve was independently associated with significant PVR after TAVI. This was also demonstrated by Seiffert et al[16] in a recent study including 537 patients treated with different models of TAVI bioprostheses (SAPIEN XT, JenaValve, Symetis, CoreValve, and Engager). Larger AVC load, particularly at the level of the LVOT inferior to the annulus (coefficient 0.146, 95% CI 0.038 to 0.253, $p = 0.008$), and type of bioprosthesis (CoreValve; coefficient 0.368, 95% CI 0.233 to 0.503, $p < 0.001$) were independently associated with PVR after TAVI. Interestingly, other types of bioprosthesis were associated with lower frequency of significant PVR after TAVI. However, increasing AVC load was associated with increased risk of PVR in all types of prosthesis if the LVOT calcification exceeded 10 mm^3. It may be difficult to correct the incidence of PVR for the design characteristics of these different prostheses.

The SAPIEN 3 improves the annular sealing by incorporating an external cuff that fills up irregularities in adjacent aortic annulus and LVOT boundaries.[17] The sealing abilities of the annular cuff can minimize oversizing and maintain valve patency without any negative impact on the residual gradient or valve area. In addition, these features may counterbalance the effect of AVC reducing the risk of PVR. Results from a few recent studies have shown promising results regarding the performance of this valve with much lower incidence of significant PVR. Jochheim et al[18] showed that the frequency of >mild PVR at discharge with the SAPIEN 3 valve was lower than that of the SAPIEN XT valve (2.0% vs8.8%, $p < 0.001$) and that use of the SAPIEN 3 valve was the only independent predictor of PVR. These results have been observed in other contemporary studies.[19,20] However, the association between the grade of PVR and the degree of AVC across the several iterations of the same valve prosthesis has not been investigated so far. In the present study, we demonstrated that the grade of significant PVR is independently associated with the degree of AVC according to Agatston calcium scoring (log-transformed Agatston score, odds ratio 3.478, 95% CI 1.424 to 8.498, $p = 0.006$). However, despite having comparable amount of AVC burden, the frequency of >mild PVR across the 3 groups of SAPIEN valve decreased significantly. These results suggest that the design features of this device may counterbalance the effects of AVC on the valve expansion.

The main limitation of our study is a single-center, nonrandomized study. This is a retrospective comparison of 3 different generations of balloon-expandable

bioprosthetic valves. The effect of learning curve and changing practices in terms of reballooning of the prosthesis or valve-in-valve implantation was not taken into consideration. In addition, the results of the present study may not be generalizable to other types of transcatheter valves. A larger population is needed to confirm the clinical end points of severity of PVR after TAVI.

In conclusion, the third generation of balloon-expandable SAPIEN 3 demonstrated lower incidence of significant PVR than the preceding SAPIEN and SAPIEN XT. Relevant PVR after TAVI remains independently associated with degree of AVC.

Disclosures

The authors have no conflicts of interest to disclose.

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